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LETTER TO THE EDITOR

Temporary renal insufficiency associated with topical tacrolimus treatment of multilocal pyoderma gangrenosum

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In renal transplant patients maintenance therapy with low dose tacrolimus and mycophenolate mofetil in combination is used to prevent renal injury and graft rejection.[1] On the other hand, calcineurin inhibitors can lead to chronic renal damage characterized by progressive and irreversible deterioration of renal function associated with interstitial fibrosis, tubular atrophy, arteriolar hyalinosis, and glomerulosclerosis in about 1% of patients.[2] Individual factors increase susceptibility to calcineurin-inhibitor related renal injury (CIRRI), such as expression of the metabolizing cytochrome P450 3A5 (CYP3A5) in kidneys although the pathogenesis of CIRRI is far from being fully understood.[3]

Topical calcineurin inhibitors are approved for the treatment of atopic dermatitis. Whole blood concentrations of the lipophilic drug tacrolimus have been < 3 ng/ml in clinical trials.[4]

Topical tacrolimus has also been used off-label to treat pyoderma gangrenosum successfully, either as monotherapy or in combination with systemic immunosuppressive regimes.[7] No renal adverse effects have been reported so far.

A 50-year-old male patient with mutilocal pyoderma gangrenosum of the lower legs since 2008 was treated by methylprednisolone 40 mg/d, enteric mycophenlate mofetil (MFF) 760 mg twice daily, pantoprazole 20 mg/d, and topical tacrolimus ointment 0.1% for the inflammatory borders of the wounds.

His medical history was remarkable for bone tuberculosis that was treated by rifampicin and isonicotinic acid hydracide (INH) until January 2012. Because of severe back pain he was taking hydromorphon (Jurnista) 16 mg/d, morphin (Sevredol) 20 mg 2x1, and metamizole (Novalgin) 3x30 gtt/d.

Laboratory controls demonstrated an increase of serum creatinine since late January. He became somnolent and was brought to the local hospital. He developed an acute renal insufficiency that was treated by dialysis. Laboratory investigations demonstrated significantly increased tacrolimus levels of 19 ng/ml 30 hours after the last topical ointment application. After repeated request, the patient stated that he applied up to 60 mg tacrolimus onto the open wounds per day. The patient underwent hemodialysis resulting in marked decrease of tacrolimus blood levels (1.2 ng/ml). Creatitinin decreased from 707.2 µmol/l to 185.6 µmol/l. Pyelonephritis could be excluded. The patient could be released from the hospital after six days with restored renal function.

Tacrolimus is an inhibitor of CYP3A4, but the patient had not taken drugs that are metabolized by this enzyme pathway.[1] The pain medication with hydromorphon is mainly metabolized by uridine diphosphate-glucuronosyl transferase. Hydromorphon can be used in patients with impaired renal function and is classified as "suggested as safe".[6] Metimazole and morphine are not metabolized by CYP3A4. Furthermore, metimazole is known as a potent inducer of this enzyme. MFF is partially metabolized by CYP3A4/5.[7] That does not prevent its use in combination with systemic tacrolimus to prevent transplant loss.

Taken together clinical and laboratory findings, temporary renal insufficiency in our patient was due to systemic absorption of significant amounts of tacrolimus used topically to support pyoderma gangrenosum therapy. After topical tacrolimus was abrogated he recovered completely. All other treatments were not changed during the patient's course. The amount of topical tacrolimus should therefore be limited in case of periulcer treatment and application on open wounds should be avoided. Since absorption can happen accidentally by ulcers tacrolimus blood levels should be determined on a regular base to keep the concentration < 3 ng/ml. As far as we know, this is the first report on topical tacrolimus causing renal injury.

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